



Whiting, P., Birnie, K., Sterne, J., Jameson, C., Skinner, R., Phillips, B., Barnfield, M., Blufpand, H., Bokenkamp, A., Grönroos, M., Jameson, C., Lankisch, P., Philips, B., Skinner, R., Sterne, J., Whiting, P. (2017). Accuracy of cystatin C for the detection of abnormal renal function in children undergoing chemotherapy for malignancy: a systematic review using individual patient data. *Supportive Care in Cancer*, 1-10. <https://doi.org/10.1007/s00520-017-4002-3>

Peer reviewed version

License (if available):
Unspecified

Link to published version (if available):
[10.1007/s00520-017-4002-3](https://doi.org/10.1007/s00520-017-4002-3)

[Link to publication record in Explore Bristol Research](#)
PDF-document

This is the author accepted manuscript (AAM). The final published version (version of record) is available online via Springer at <https://link.springer.com/article/10.1007/s00520-017-4002-3>. Please refer to any applicable terms of use of the publisher.

University of Bristol - Explore Bristol Research

General rights

This document is made available in accordance with publisher policies. Please cite only the published version using the reference above. Full terms of use are available:
<http://www.bristol.ac.uk/red/research-policy/pure/user-guides/ebr-terms/>

Accuracy of cystatin C for the detection of abnormal renal function in children undergoing chemotherapy for malignancy: A systematic review using individual patient data

Penny Whiting^{1, 2}, Kate Birnie², Jonathan A C Sterne², Catherine Jameson², Rod Skinner⁴, Bob Phillips³, and the Cystatin C in Childhood Cancer Collaboration Group*

*For members of the CCiCCC group see the appendix

¹NIHR CLAHRC West, University Hospitals Bristol NHS Foundation Trust, 9th Floor, Whitefriars, Lewins Mead, Bristol BS1 2NT

²School of Social and Community Medicine, University of Bristol, Canynge Hall, 39 Whatley Road, Bristol, BS8 2PS, United Kingdom

³Centre for Reviews and Dissemination, University of York, York, UK, YO10 5DD

⁴Department of Paediatric and Adolescent Haematology / Oncology and Children's BMT Unit, Great North Children's Hospital, Royal Victoria Infirmary, Newcastle upon Tyne, NE1 4LP.

Word count: 3476 words

Running head: SR of cystatin C in children undergoing chemotherapy

Key words: systematic review, children, chemotherapy, cystatin C, diagnostic accuracy

Acknowledgements

This project was funded by the Medical Research Council (G0801405/1). JS was supported by National Institute for Health Research (NIHR) Senior Investigator Awards (NF-SI-0611-10168). KB was supported by a Medical Research Council UK fellowship (RD1826). RSP is supported by the National Institute for Health Research (NIHR) Post Doctoral Award (PDF-2014-07-072). PW is funded by a National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care West (NIHR CLAHRC West). The sponsor had no role in study design; in the collection, analysis, and interpretation of data; in the

writing of the report; or in the decision to submit the paper for publication. All authors had full access to all the data in the study.

Abstract (250 words)

Purpose

We conducted a systematic review and individual patient data (IPD) meta-analysis to examine the utility of cystatin C for evaluation of glomerular function in children with cancer.

Methods

Eligible studies evaluated the accuracy of cystatin C for detecting poor renal function in children undergoing chemotherapy. Study quality was assessed using QUADAS-2. Authors of four studies shared IPD. We calculated the correlation between log cystatin C and GFR stratified by study and measure of cystatin C. We dichotomized the reference standard at GFR 80 ml/min/1.73m² and stratified cystatin C at 1mg/l, to calculate sensitivity and specificity in each study and according to age group (0-4, 5-12 and ≥13 years). We used logistic regression to estimate the association of impaired renal function with log cystatin C and quantified diagnostic accuracy using the Area Under the ROC Curve (AUC).

Results

Six studies, which used different test and reference standard thresholds, suggested that cystatin C has the potential to monitor renal function in children undergoing chemotherapy for malignancy. IPD data (504 samples, 209 children) showed that cystatin C has poor sensitivity (63%) and moderate specificity (89%). The AUC for the combined data set was 0.890 (95% CI 0.826, 0.951). Diagnostic accuracy appeared to decrease with age.

Conclusions

Cystatin C has better diagnostic accuracy than creatinine as a test for glomerular dysfunction in young people undergoing treatment for cancer. Diagnostic accuracy is not sufficient for it to replace current reference standards for predicting clinically relevant impairments that may alter dosing of important nephrotoxic agents.

Introduction

Causes of glomerular dysfunction in children with cancer include direct and indirect effects of the malignant process and its treatment, and a range of potentially additive side effects from chemotherapy, radiotherapy, surgery, immunotherapy or supportive treatment.

Glomerular impairment is variable in severity and potential reversibility. Renal dysfunction frequently impacts on the management of children with cancer, and in particular may have important implications for the ability to deliver optimal chemotherapy.^{1,2}

It is important to evaluate glomerular function in children with cancer since glomerular filtration is a major determinant of renal excretion and hence the systemic clearance of some important chemotherapy (e.g. carboplatin) and supportive care drugs (e.g. aciclovir).² Accurate assessment is important since the therapeutic index of many of these drugs is narrow, with even relatively small differences in systemic exposure leading to potential under-treatment and hence poorer anti-tumour efficacy or over-dosage and risk of significant toxicity. However, current approaches to measuring glomerular function in children have important limitations, including their accuracy and practicability.³ A simple, reliable, blood test capable of evaluating glomerular function accurately would be valuable.

Plasma cystatin C is a promising new serum marker for monitoring renal function. Several studies have investigated its utility as a measure of glomerular function, and some have suggested that it should be used in clinical practice. However, we are not aware of any previous systematic review of these studies.

Individual patient data (IPD) pooled analysis of data from randomized trials can facilitate consistent approaches to the control of patient characteristics at baseline and has particular advantages for subgroup analyses.^{4,5} It has recently been promoted for the synthesis of diagnostic accuracy data, but few reviews of diagnostic test accuracy data have used IPD.⁶ Potential benefits of diagnostic IPD analysis include the use of information about the receiver operating characteristic (ROC) curve that is not captured in summary (2x2) tables of diagnostic accuracy, the potential to examine diagnostic accuracy within patient subgroups, and enhanced statistical precision compared with analyses of individual studies. We

examined the utility of cystatin C for evaluation of glomerular function in children with cancer based on IPD combined from four studies, and compared results to those obtained using summary data.

Methods

Literature searches

Diagnostic test accuracy (DTA) studies were identified by searching MEDLINE, EMBASE, Biosis, Science Citation Index, and LILACS from inception to June 2009. The MEDLINE search was updated in March 2015. In addition, information on studies in progress, unpublished research or research reported in the grey literature was sought by searching a range of relevant databases including Zetoc, SIGLE, Dissertation Abstracts, the metaRegister of Controlled Trials, NTIS and the GrayLit network. The search strategy was based on combining terms for the index test (cystatin C) and target condition (renal function), and limiting results to studies in children. Full details of the search strategy are available from the authors on request.

Selection of studies

Studies that were eligible for inclusion evaluated the accuracy of cystatin C for the detection of poor renal function/reduced GFR in children undergoing chemotherapy against a reference standard consisting of 24-hour urine collection, inulin clearance, or radio-isotope scans. Two reviewers independently screened the search results. Full text papers were assessed for inclusion by one reviewer and checked by a second. Disagreements were resolved through consensus.

Extraction of summary data and quality assessment

Summary data on participants, index test, reference standard, 2x2 tables of diagnostic accuracy, sensitivity, specificity and measures of correlation were extracted from the published study reports using data extraction forms developed using Microsoft Access. Where available, data stratified according to age were extracted separately for different age

groups. Study quality was assessed using the QUADAS-2 tool.⁷ This includes domains covering bias due to selection of participants, index test, reference standard and flow and timing. The first three domains are also assessed in terms of applicability to the review question. Data extraction and quality assessment were carried out by one reviewer and checked by a second.

Individual Patient Data

Authors of the published studies were contacted and invited to take part in the “Cystatin C in Childhood Cancer Collaboration” (CCiCCC). They were asked to share the individual patient data (IPD) from their study to facilitate analyses that could not be conducted based on summary data alone. Facilities were set up to allow secure transfer of data. Authors were asked to upload a dataset containing the following data, if available: underlying tumour type, chemotherapy type and date of last cycle, other treatment, comorbidity, age, gender, height, weight, BMI, number of samples tested for cystatin C, numerical results for each cystatin C test, dates of each cystatin C test, number of samples tested using the reference standard, numerical results for each reference standard assessment, dates of each reference standard assessment, other tests conducted, results of all other tests, if the patient did not receive both the cystatin C test and reference standard, reasons for this. The data request form is available as a web appendix.

Analysis of summary data

There were insufficient data to allow diagnostic meta-analysis of summary data, so instead a narrative synthesis was presented. Measures of correlation between cystatin C and GFR were summarized. Ranges of sensitivity and specificity were calculated. Estimates of sensitivity and specificity were plotted in ROC space.

Analysis of individual patient data

We standardized definitions and categorizations of variables across studies as far as practicable, and agreed a common set of variables to be combined from each study. Data were combined into a single dataset with an additional variable for study number (1 to 4).

When considering cystatin C and creatinine as continuous variables, we log transformed the measures because their distributions were right-skewed. We investigated the association between cystatin C and GFR (the reference standard): we calculated the correlation between log cystatin C and GFR, stratified by study and by cystatin C sample number if multiple measures were made in the same individual. For further analyses we selected the first sample per person. We dichotomized the GFR reference standard at 80 ml/min/1.73m², with values below this indicating impaired renal function. We dichotomized cystatin C at 1mg/l, with values above this indicating poor renal function. We used 2x2 tables of dichotomized GFR and cystatin C to calculate sensitivity and specificity at these thresholds in each study. We used fixed-effect logistic regression to estimate the association of impaired renal function (GFR) with the serum markers of renal function (cystatin C and creatinine). For these regression models, log cystatin C and log creatinine were converted into z-scores with mean zero and standard deviation (SD) one in the combined dataset, enabling comparisons of their effects for an equivalent one SD change in each serum marker. We fitted separate models for each study and a combined model across the studies that included an indicator variable for study number. We quantified diagnostic accuracy using the Area Under the ROC Curve (AUC) in models that included (i) log cystatin C, (ii) log creatinine and (iii) both log cystatin C and log creatinine, for the studies for which data on both of these variables were available. To investigate variation in diagnostic accuracy with age we fitted separate models for different age groups (0-4, 5-12 and ≥13 years). As sensitivity analyses, we: (1) investigated different cystatin C cut points to establish what threshold would provide sensitivity greater than 0.98 and (2) allowed for repeated measures of samples within patients, using the 'somersd' command after multilevel mixed-effects logistic regression model in Stata version 14 to calculate the AUC.

Results

The searches identified 2621 studies, of which six diagnostic cohort studies met inclusion criteria.⁸⁻¹³ Two of these were available only in abstract form.^{9,12} The six studies included 342 children (range 28 to 99) and more than 545 samples (range 31 to 276; not reported in one study). Mean age ranged from 3.2 to 11.3 years and the proportion of girls ranged from 26% to 64%. The studies included patients with various different cancers. Only one study

reported on chemotherapy regimen, which varied between children. Five studies used immunonephelometric methods to measure cystatin C concentration; the remaining study did not report on how cystatin C was measured.⁹ Three studies did not use a threshold to dichotomize cystatin C test result⁸⁻¹⁰; the threshold varied between the remaining three studies. Four studies used radioisotope plasma clearance techniques as the reference standard to measure GFR as an indicator of kidney function.^{8-10,12} Two studies used a threshold of $<90\text{ml/min}/1.73\text{m}^2$ and one a threshold of $<100\text{ml/min}/1.73\text{m}^2$ as an indicator of impaired kidney function; the other did not dichotomize GFR. One study used 24-hour urine collection creatinine clearance ratio as an estimate of GFR, with the threshold for normal GFR varying based on age and gender.¹³ The final study used inulin clearance measured using blood sampling at various time points after injection of polyfructosan, with a threshold of $<90\text{ml/min}/1.73\text{m}^2$ indicating abnormal GFR. A summary of the six published studies is provided in Table 1.

The results of the QUADAS-2 assessment are summarized in Web Figure 1. All studies were judged at low or unclear risk of bias and concerns regarding applicability for all domains. Two studies were judged at low risk of bias for patient spectrum;^{11,13} four were judged at unclear risk of bias as they did not provide sufficient information on how patients were enrolled into the studies. Three studies were judged at unclear risk of bias for the flow and timing domain as it was unclear whether all enrolled patients contributed to the analysis. The only concern regarding applicability was one study¹² that used a higher reference standard threshold than commonly used to define an abnormal glomerular filtration rate ($<100\text{ mL/min}/1.73\text{m}^2$).

Summary Data

Three studies provided measures of correlation between cystatin C and the reference standard (Web Table 1).^{9,10,13} Two studies suggested a strong negative correlation and one suggested a weaker correlation. Three studies, including one that provided correlation data,¹³ reported data on sensitivity and specificity.¹¹⁻¹³ One of these did not provide sufficient data to construct a 2x2 table of test performance as it was unclear how many patients were classed as having normal/abnormal GFR.¹² One study did not provide summary data on

either correlation or accuracy.⁸ Estimates of sensitivity and specificity plotted in ROC space from the three studies which provided data on the accuracy of cystatin C are shown in Figure 1.¹¹⁻¹³ One study provided estimates of sensitivity and specificity for two different age groups and so contributes two points to the graph.¹³ Sensitivity ranged from 39 to 100%, specificity ranged from 79 to 94%.

IPD data

Four of the six studies agreed to become members of the 5C collaboration and shared their data.^{8,10,11,13} The number of participants and age of included children showed some variation from that reported in the summary data reports of these studies (Table 1). The total number of participants was 229 (range 22 to 84 per study) and the number of samples was 504 (range 68 to 262 per study). The median age at first measure ranged from 2.8 to 12.1 years. In the IPD, median cystatin C in the individual studies ranged from 0.74 mg/l to 0.89 mg/l. The median GFR ranged from 86.3 ml/min/1.73m² to 130.0 ml/min/1.73m². The correlations between log cystatin C and GFR for the first sample per person ranged from -0.454 to -0.713 (Web Table 1). Correlations between log cystatin C and GFR on the repeated samples, where available, were similar.

Estimates of sensitivity and specificity at a cystatin C threshold of 1 mg/l are shown in Table 2 and Figure 3, which also shows individual ROC plots for each study. Sensitivity ranged from 53% to 75% and specificity from 86% to 100%. The estimates combining IPD from all four studies were sensitivity 63.2% (95% CI 46.0%, 78.2%) and specificity 88.9% (83.6%, 93.0%).

Estimates of area under the ROC curve (AUC) for cystatin C were 0.915 (95% CI 0.829, 1.00) for the Lankisch study,¹³ 0.862 (0.775, 0.950) for the Barnfield study¹⁰ and 0.792 (0.427, 1.00) for the Blufpand study¹¹ (Table 3). It was not possible to construct an ROC curve for the Gronroos study⁸ as there were no events of GFR<80ml/min/1.73m². There was little evidence that the AUC varied between studies (interaction p=0.77). The AUC for the combined data set, based on the three studies for which individual ROC curves could be constructed, was 0.890 (95% CI 0.826, 0.951) which is not considered sufficiently accurate for clinical use. Diagnostic accuracy of cystatin C appeared to be highest in the younger age

group (AUC 0.945, 95% CI 0.895, 0.996) and to decrease with age (Figure 2). For the Barnfield study diagnostic accuracy was substantially greater for cystatin C (AUC 0.862) than for creatinine (0.681) and was not improved in the model containing both variables (0.861) compared with cystatin C alone (Table 3). For the Blufpand study, diagnostic accuracy was also substantially greater for cystatin C (0.792) than for creatinine (0.696) and was improved in the model containing both variables (0.883) compared with cystatin C alone. In the Lankisch study diagnostic accuracy for cystatin C was 0.915, but data on creatinine were not available.

The odds ratios from all logistic regression models are shown in Web Table 2. The unadjusted odds ratios per SD increase in log cystatin C for impaired renal function (GFR) were 9.0 (95% CI: 3.1, 26.0; $p < 0.001$) in the Barnfield study, 4.6 (1.1, 19.3; $p = 0.039$) in the Blufpand study and 7.5 (3.0, 18.9; $p < 0.001$) in the Lankisch study. The unadjusted odds ratios per SD increase in log creatinine were lower: 2.2 (1.3, 3.8; $p = 0.006$) and 0.4 (0.1, 1.7; $p = 0.219$) in the Barnfield and Blufpand data, respectively. Odds ratios were not substantially changed in models that contained both cystatin C and creatinine. Combined across studies, the odds ratios per SD increase in log cystatin C were 7.4 (4.0, 13.8; $p < 0.001$) based on the first measure and 9.3 (5.8, 14.9; $p < 0.001$) based on all measures. The odds ratio per SD increase in log cystatin C was 15.0 (3.1, 71.9) in younger children and 6.1 (2.2, 16.7) in older children (p for interaction = 0.727).

Results from sensitivity analyses showed that estimated sensitivity for a cystatin C threshold of >0.7 mg/l was 100%, but the corresponding specificity was only 31.6% and more than 70% of patients would be classified as having 'elevated' cystatin C at this threshold. The AUC from the model for cystatin C using all data and allowing for repeated measures per person was 0.902 (95% CI 0.861, 0.942); the odds ratio per SD increase in log cystatin C in this model was 9.3 (5.8, 14.9; $p < 0.001$; Web Table 2).

Discussion

Summary of findings

We conducted a systematic review and meta-analysis of published summary data and individual patient data from diagnostic test accuracy studies of cystatin C for diagnosis of impaired renal function in children with cancer. The six available published reports suggested that cystatin C has the potential to monitor renal function in children undergoing chemotherapy for malignancy, but they used different test and reference standard thresholds, and the summary data were impossible to synthesize quantitatively. The IPD analyses provided important additional information and led to clearer conclusions than those possible with published summary data. They showed that at a threshold of $>1\text{mg/l}$ cystatin C has limited sensitivity (63%) and moderate specificity (89%) for diagnosis of impaired renal function. Using a threshold which achieved sensitivity 0.98 ($>0.7\text{ mg/l}$), 70% of the tested population would have an 'elevated' cystatin C and require further testing with a reference standard test. Diagnostic accuracy for cystatin C was consistent across studies. For the two studies for which data were available, diagnostic accuracy of cystatin C was clearly greater than that of creatinine. However diagnostic accuracy may not be sufficient to justify the use of cystatin C as a screening test for glomerular dysfunction, because of the practical implications of incorrect classification of renal function, or the large proportion of children in whom a second, definitive test would be required after cystatin C testing. These include under-dosing patients with a reduction in anti-cancer efficacy in whom the test incorrectly reports renal impairment, and excessive dosing with high risks of severe chemotherapy toxicities in those who are incorrectly reported as having sufficient renal function.

Strengths and limitations

The comprehensive and efficient use of IPD data, collected by a collaborative effort from the 5C group, has allowed us to clearly describe the limits of uncertainty with cystatin C in childhood cancer and conclude that this test is not suitable for routine use. Limitations of our review include the small number of studies available on this topic and that we were only able to obtain IPD data for four of the six identified studies, all of which had very small sample sizes (range 22 to 84 children). It is unclear why the other groups declined to participate. The summary data available were insufficient to perform standard meta-analysis and so we were unable to compare the results from summary data meta-analysis with IPD meta-analysis. There were some discrepancies between what had been reported in

the publications of the studies and the IPD that were provided to us, for example the number of samples. While studies investigating other markers are being developed, consideration should be given by clinical researchers to regularly enter into collaboration with other academics, guided by partners skilled in meta-analysis, to produce results which are more precise and globally applicable than any one study group would achieve.

Comparison with existing literature

Cystatin C has been promoted as a marker of renal function in a variety of conditions, for example post-renal transplant in adults¹⁴ or children,¹⁵ or in adults with malignancy.¹⁶ Other uses for the marker include the prediction of mortality in adult populations with and without renal impairment,¹⁷ with high risk conditions such as type 2 diabetes¹⁸ or in critical care units.¹⁹ The clinical utility of cystatin C differs according to the indication.^{18,19} The accuracy of cystatin C based measurements is consistently better than those based on creatinine alone, and may be reasonable to use at a population based level.²⁰ However, these measurements have previously been shown not to be useful as a basis for chemotherapy dosing decisions.²¹

These findings place cystatin C in a similar situation to existing tests for renal impairment, which all have important challenges in their regular clinical use. Routinely measured creatinine has insufficient accuracy as a serum marker for renal function, especially in children.²² Serum concentrations of creatinine and particularly urea are insensitive, with abnormal values not seen until the glomerular filtration rate (GFR) has fallen by 30-50%.⁸ GFR can be estimated from formulae including serum creatinine concentration and patient height but their utility in determining GFR in children with cancer has been shown to be low.^{23,24} The creatinine clearance method requires accurately timed urine collections which are difficult to achieve reliably in children, overestimates GFR due to tubular secretion of creatinine and has been shown to be poorly reproducible.²⁵ The inulin clearance method is technically difficult since inulin is not routinely measured in clinical laboratories, and requires an intravenous inulin infusion and again, a timed urine collection. Where an accurate measurement of glomerular function is required to dose chemotherapy, it remains important to use plasma radioisotope clearance (e.g. ⁵¹Cr-EDTA clearance), despite the logistical limitations and exposure to low dose radiation.²⁵

Implications for future research

Further research could examine whether particular clinical situations alter the clinical utility of cystatin C testing. Our data were insufficient to determine if the diagnostic accuracy of cystatin C varied between risk groups, for example those exposed to multiple courses of nephrotoxic agents, who had documented episodes of acute kidney injury during their therapy, or with high body mass index. Such research would benefit from multi-institutional collaboration, as clinically important glomerular dysfunction is uncommon in children with cancer.

Conclusions

Cystatin C is more useful than creatinine as a screening test for glomerular dysfunction in children and young people undergoing treatment for cancer. However, diagnostic accuracy is not sufficiently for it to replace current reference standards for predicting clinically relevant impairments that may alter the dosing of important nephrotoxic agents. This conclusion could only be firmly reached after combination of individual patient data from multiple studies. A limited reading of selected publications could lead clinicians into using this test as an easy and effective alternative to assessments using the reference standard, and inadvertently producing incorrect decisions leading to avoidable renal impairment or under-dosing of anti-cancer agents. Advancing clinical care requires a clear understanding of the value of innovations: describing the limitations of new interventions and technologies is as important as extolling their benefits, and preventing the uptake of unhelpful approaches is a key to effective care as rapidly rolling out beneficial programmes of care. Collaborative effort by multinational groups to share and combine data facilitate the evaluations required to make judgments about the role of new tests and interventions in clinical care.

References

1. Blufpand HN, Hes N, Bokenkamp A, van de Wetering MD, Kaspers GJ. Diversity in renal function monitoring and dose modifications during treatment for childhood cancer: a call for standardization. *Pediatr Blood Cancer* 2014; **61**(2): 337-44.
2. Skinner R. Nephrotoxicity--what do we know and what don't we know? *J Pediatr Hematol Oncol* 2011; **33**(2): 128-34.
3. Bardi E, Olah AV, Bartyik K, et al. Late effects on renal glomerular and tubular function in childhood cancer survivors. *Pediatric Blood & Cancer* 2004; **43**(6): 668-73.
4. Riley RD, Lambert PC, Abo-Zaid G. Meta-analysis of individual participant data: rationale, conduct, and reporting. *Bmj* 2010; **340**: c221.
5. Stewart LA, Tierney JF. To IPD or not to IPD? Advantages and disadvantages of systematic reviews using individual patient data. *Evaluation & the health professions* 2002; **25**(1): 76-97.
6. Broeze KA, Opmeer BC, Bachmann LM, et al. Individual patient data meta-analysis of diagnostic and prognostic studies in obstetrics, gynaecology and reproductive medicine. *BMC medical research methodology* 2009; **9**: 22.
7. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011; **155**(8): 529-36.
8. Gronroos MH, Jahnukainen T, Irjala K, et al. Comparison of glomerular function tests in children with cancer. *Pediatric Nephrology* 2008; **23**(5): 797-803.
9. Aydin F, Tezcan G, Gungor O, et al. Can serum cystatin C reflect the glomerular filtration rate accurately in pediatric patients under chemotherapeutic treatment? A comparative study with Tc-99m DTPA two-plasma sample method. *NuclMed Commun* 2010; **31**(4): 301-6.
10. Barnfield MC, Burniston MT, Reid U, Graham AM, Henderson M, Picton SV. Cystatin C in assessment of glomerular filtration rate in children and young adults suffering from cancer. *Nuclear medicine communications* 2013; **34**(6): 609-14.
11. Blufpand HN, Tromp J, Abbink FC, et al. Cystatin C more accurately detects mildly impaired renal function than creatinine in children receiving treatment for malignancy. *Pediatr Blood Cancer* 2011; **57**(2): 262-7.
12. Djemli A, Merouani A, Lambert R, et al. Cystatin C: A marker of kidney function in pediatric oncology. *Clinical Chemistry* 2005; **51**: A34-A.
13. Lankisch P, Wessalowski R, Maisonneuve P, Haghgu M, Hermsen D, Kramm CM. Serum cystatin C is a suitable marker for routine monitoring of renal function in pediatric cancer patients, especially of very young age. *Pediatric Blood & Cancer* 2006; **46**(7): 767-72.
14. Harman G, Akbari A, Hiremath S, et al. Accuracy of cystatin C-based estimates of glomerular filtration rate in kidney transplant recipients: a systematic review. *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association* 2013; **28**(3): 741-57.
15. de Souza V, Cochat P, Rabilloud M, et al. Accuracy of different equations in estimating GFR in pediatric kidney transplant recipients. *Clinical journal of the American Society of Nephrology : CJASN* 2015; **10**(3): 463-70.
16. Terpos E, Christoulas D, Kastiris E, et al. The Chronic Kidney Disease Epidemiology Collaboration cystatin C (CKD-EPI-CysC) equation has an independent prognostic value for overall survival in newly diagnosed patients with symptomatic multiple myeloma; is it time

- to change from MDRD to CKD-EPI-CysC equations? *European journal of haematology* 2013; **91**(4): 347-55.
17. Hingorani S, Pao E, Schoch G, Gooley T, Schwartz GJ. Estimating GFR in adult patients with hematopoietic cell transplant: comparison of estimating equations with an iohexol reference standard. *Clinical journal of the American Society of Nephrology : CJASN* 2015; **10**(4): 601-10.
 18. Ito R, Yamakage H, Kotani K, et al. Comparison of cystatin C- and creatinine-based estimated glomerular filtration rate to predict coronary heart disease risk in Japanese patients with obesity and diabetes. *Endocrine journal* 2015; **62**(2): 201-7.
 19. Nejat M, Pickering JW, Walker RJ, et al. Urinary cystatin C is diagnostic of acute kidney injury and sepsis, and predicts mortality in the intensive care unit. *Crit Care* 2010; **14**(3): R85.
 20. Swedish Council on Health Technology Assessment. Methods to Estimate and Measure Renal Function (Glomerular Filtration Rate) A Systematic Review. 2012. <http://sbu.se/en/Published/Yellow/Methods-to-Estimate-and-Measure-Renal-Function-Glomerular-Filtration-Rate/>.
 21. Shlipak MG, Matsushita K, Arnlov J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *The New England journal of medicine* 2013; **369**(10): 932-43.
 22. Bardi E, Bobok I, Olah AV, Olah E, Kappelmayer J, Kiss C. Cystatin C is a suitable marker of glomerular function in children with cancer.[see comment]. *Pediatric Nephrology* 2004; **19**(10): 1145-7.
 23. Skinner R, Cole M, Pearson AD, et al. Inaccuracy of glomerular filtration rate estimation from height/plasma creatinine ratio. *Archives of disease in childhood* 1994; **70**(5): 387-90.
 24. Bernhardt MB, Moffett BS, Johnson M, Tam VH, Thompson P, Garey KW. Agreement among measurements and estimations of glomerular filtration in children with cancer. *Pediatr Blood Cancer* 2015; **62**(1): 80-4.
 25. Soveri I, Berg UB, Bjork J, et al. Measuring GFR: a systematic review. *American Journal of Kidney Diseases* 2014; **64**(3): 411-24.

Acknowledgments

We would like to thank Rebecca Beynon for her help in screening search results and assessing studies for inclusion in the systematic review.

Declaration of interests

None of the authors has any conflicts of interest.

Author contributions

PW, JS and BP conceived the idea for the study and drafted the protocol. PW and CJ identified studies for inclusion, extracted data and performed the risk of bias assessment. PW performed the synthesis of the summary data, KB and JACS performed the analysis of the IPD data. BP and RS provided clinical input. Members of the 5C collaboration shared IPD data from their studies. All authors revised the manuscript for important intellectual content and approved the final version of the manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Appendix: Members of the cystatin C in Childhood Cancer Collaboration Group

Mark Barnfield (St James's University Hospital, Leeds, England), Kate Birnie (University of Bristol, England), Hester Blufpand (VU University Medical Center, Amsterdam, The Netherlands), Arend Bokenkamp (VU University Medical Center, Amsterdam, The Netherlands), Marika Grönroos (Turku University Hospital, Finland), Catherine Jameson (University of Bristol, England), Petra Lankisch (University Hospital Düsseldorf, Germany), Bob Philips (University of York, England), Rod Skinner (Great North Children's Hospital, Newcastle upon Tyne, England), Jonathan Sterne (University of Bristol, England), Penny Whiting (University of Bristol, England).

Table 1: Summary of included studies that provided summary data

| Summary data from published papers | | | | | | | |
|----------------------------------------------------------|----------------|-----------------------------|------------------------------------------|---------------|---------------------------------------|-----------------------------------------------------------------|----------------------------------------------------------------|
| Study | Country | N patients (samples) | Median or mean age (range), years | % Male | Cystatin C Threshold (mg/l) | Reference standard measure (GRF) | Reference standard threshold (ml/min/1.73m²) |
| Aydin (2010) ⁹ | Turkey | 31 (31) | 8.2 (2-16) | 32 | Not stated | Radioisotope plasma clearance techniques | NA |
| Barnfield (2013) ¹⁰ | UK | 99 (NR) | 11.9* (0.5-23.6) | 74 | No threshold used | Radioisotope plasma clearance techniques | NA |
| Blufpand (2011) ¹¹ | Holland | 68 (276) | 3.2 (1.4-7.8) [†] | 74 | <90 ± | Inulin clearance | <90 |
| Djemli (2005) ¹² | Canada | 28 (46) | 9.4* (2-20) | 36 | >0.675 | Radioisotope plasma clearance techniques | <100 |
| Gronroos (2008) ⁸ | Finland | 36 (112) | 11.3* (2.8-23.9) | 42 | No threshold used | Radioisotope plasma clearance techniques | <90 |
| Lankisch (2006) ¹³ | Germany | 80 (80) | 8.7* (0.2-17.9) | 56 | 0-1y: >1.17 >1y: >0.95 | 24-Hour urine collection; creatinine clearance ratio | 0-1y: <64, 1-13y: <120 14-18y: male <97, female <88 |
| Individual patient data (IPD) provided to authors | | | | | | | |
| Study | Country | N patients (samples) | Median or mean age (range), years | % Male | Median (IQR) cystatin C (mg/l) | Median (IQR) reference standard ml/min/1.73m² | Reference standard threshold (ml/min/1.73m²) |
| Aydin (2010) ⁹ | Turkey | NA | NA | NA | N/A | N/A | N/A |
| Barnfield (2013) ¹⁰ | UK | 84 (262) | 12.1 (0.5-21.6) | 69 | 0.89 (0.75, 1.04) | 86.3 (72.2, 101.5) | <80 |
| Blufpand (2011) ¹¹ | Holland | 43 (68) | 2.8 (0.1-16.9) | 63 | 0.80 (0.69, 0.92) | 114.9 (97.4, 129.0) | <80 |
| Djemli (2005) ¹² | Canada | NA | NA | NA | N/A | N/A | N/A |
| Gronroos (2008) ⁸ | Finland | 22 (94) | 8.5 (2.8-17.7) | 41 | 0.74 (0.65, 0.84) | 113.1 (100.3, 133.0) | <80 |
| Lankisch (2006) ¹³ | Germany | 80 (80) | 8.2 (0.2-18.3) | 56 | 0.80 (0.70, 1.00) | 130.0 (95.5, 147.0) | <80 |

N: Number; NA: Not available; * indicates mean age, all other ages are medians; † Reported in paper as range, but IPD data suggests interquartile range (IQR); ± the cystatin C-based GFR estimate was calculated as $\log \text{eGFR}_{\text{cys}} (\text{ml/min/1.73 m}^2) = 1.962 + [1.123 \times \log (1/\text{cystatin C (mg/dl)})]$

Table 2: Estimates of sensitivity and specificity from summary data compared to estimates from IPD data

| Study | Summary Data | | | IPD Data | | |
|--------------------------------|-----------------------------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| | Cystatin C threshold | Sensitivity (95% CI) | Specificity (95% CI) | Cystatin C threshold | Sensitivity (95% CI) | Specificity (95% CI) |
| Barnfield (2013) ¹⁰ | NA | NA | NA | ≥1mg/L | 53% (29%, 76%) | 86% (75%, 93%) |
| Blufpand (2011) ¹¹ | 90mg/L | 57% (29%, 82%) | 94% (84%, 99%) | ≥1mg/L | 67% (9%, 99%) | 93% (80%, 98%) |
| Djemli(2005) ¹² | 0.675mg/L | 100% | 79 | ≥1mg/L | NA | NA |
| Gronroos (2008) ⁸ | NA | NA | NA | ≥1mg/L | NA | 100% (85%, 100%) |
| Lankisch(2006) ¹³ | 1-11month >1.17mg/L, >1year >0.95 | 39% (22%, 58%) | 84% (70%, 93%) | ≥1mg/L | 75% (48%, 93%) | 86% (75%, 93%) |
| Overall | | | | | 63.2% (46.0%, 78.2%) | 88.9% (83.6%, 93.0%) |

Table 3 AUC for cystatin C, creatinine, and cystatin C and creatinine in the same model, for predicting GFR for the IPD datasets

| Study | AUC (95% CI) | | |
|--------------------------------|----------------------|----------------------|----------------------|
| | Cystatin C | Creatinine | Cystatin C and |
| | | | Creatinine |
| Barnfield (2013) ¹⁰ | 0.862 (0.775, 0.950) | 0.681 (0.521, 0.840) | 0.861 (0.772, 0.948) |
| Blufpand (2011) ¹¹ | 0.792 (0.427, 1.000) | 0.696 (0.270, 1.00) | 0.883 (0.692, 1.000) |
| Gronroos (2008) ⁸ | N/A | N/A | N/A |
| Lankisch (2006) ¹³ | 0.915 (0.829, 1.000) | N/A | N/A |

Notes: The GFR reference standard was dichotomized at GFR 80 ml/min/1.73m². Cystatin C and creatinine were log transformed. The Gronroos study was excluded because there were no events of GFR<80 ml/min/1.73m². Creatinine data were not available for analysis in our IPD dataset for the Lankisch study as we believe it may have also been used to calculate GFR.

Figure 1: Summary ROC plot showing estimates of sensitivity and specificity from studies reporting summary data

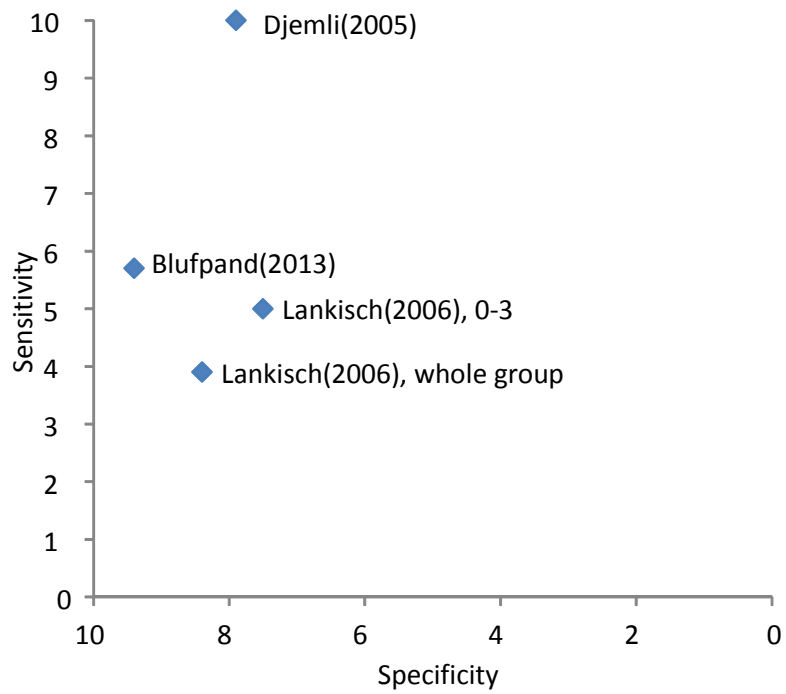


Figure 2: ROC plots for cystatin C for predicting GFR for the IPD datasets, stratified by study with additional plot showing summary estimates of sensitivity and specificity

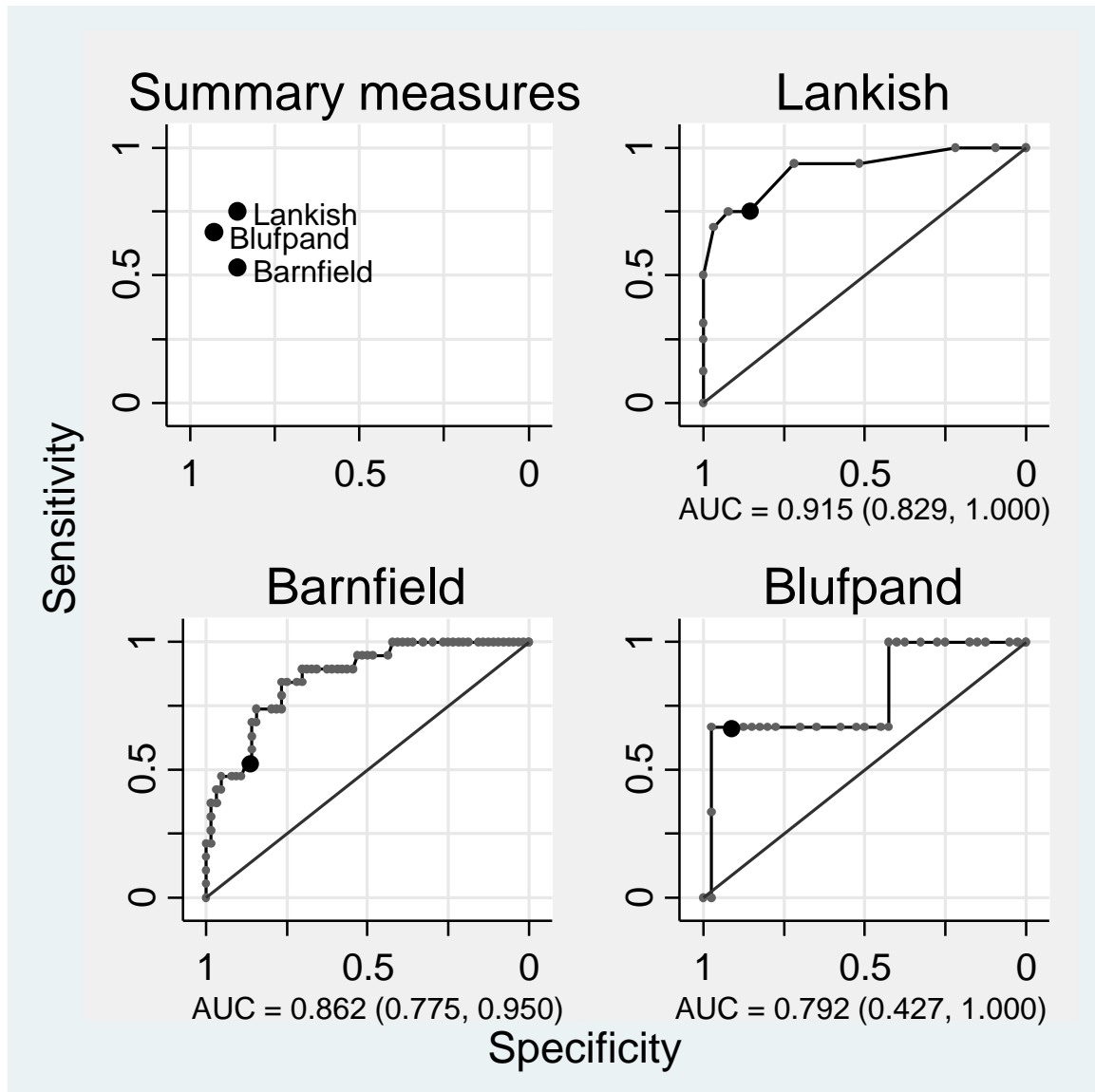
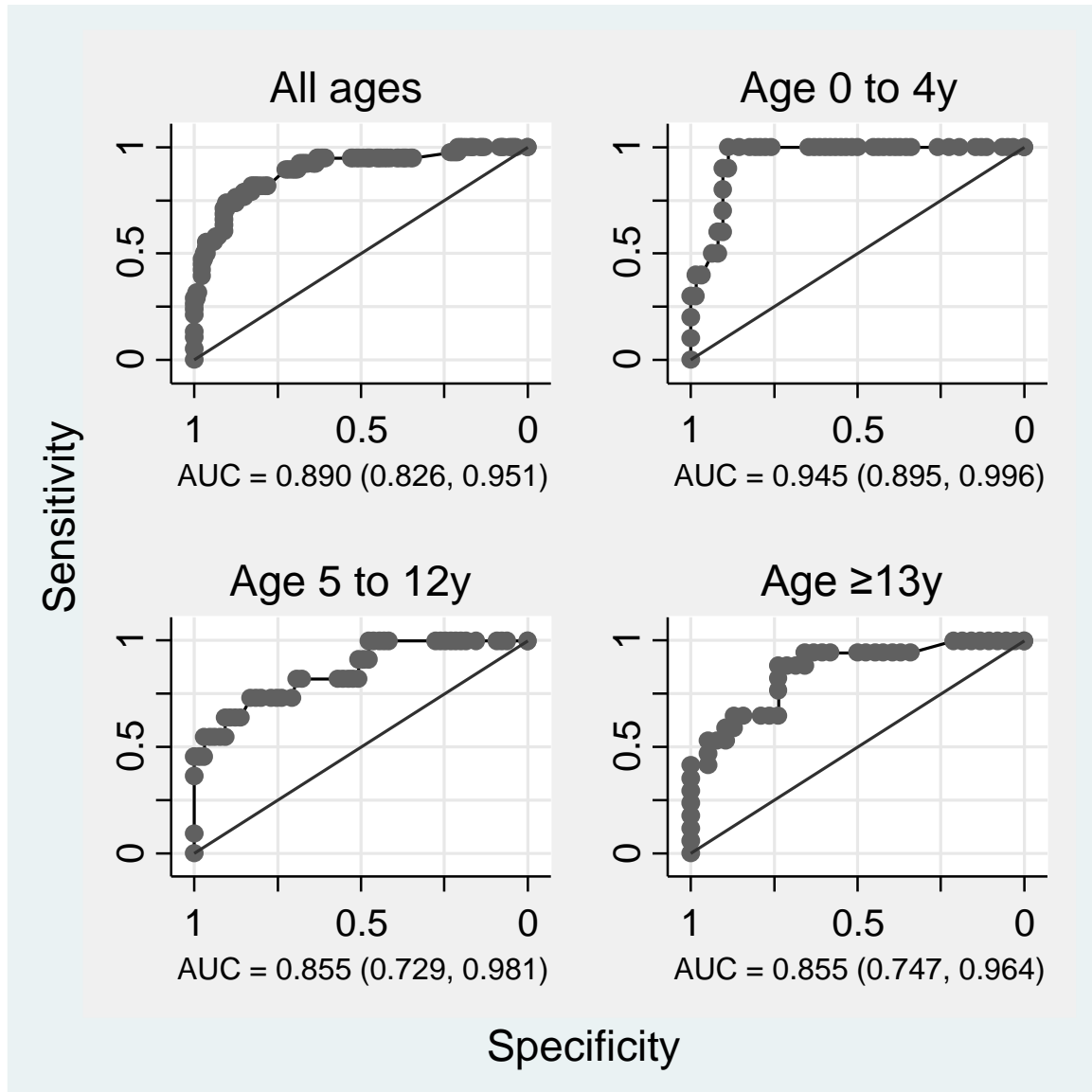


Figure 3: ROC plots for cystatin C for predicting GFR for the combined IPD dataset stratified according to age group



Web Table 1: Estimates of correlation between cystatin C and GFR

| Study | Summary Data | | IPD data, natural log transformed cystatin C | |
|--------------------------------|------------------------|-----------------------------------|----------------------------------------------|-------------------------|
| | N (samples) | Correlation | N | Correlation(95% CI) |
| Aydin (2010) ⁹ | 31 (31) | -0.42 | NA | |
| Barnfield (2013) ¹⁰ | 99 (NR) | 0.66 for reciprocal of cystatin C | 83 | -0.713 (-0.805, -0.588) |
| Blufpand (2011) ¹¹ | 68 (276) | Not reported | 43 | -0.568 (-0.742, -0.323) |
| Djemli(2005) ¹² | 28 (46) | Not reported | NA | |
| Gronroos (2008) ⁸ | 36 (112) | Not reported | 22 | -0.454 (-0.735, -0.040) |
| Lankisch(2006) ¹³ | 80 (80), whole sample | -0.70 | 80 | -0.689 (-0.789, -0.553) |
| | 14 (14), age 0-3 years | -0.74 | | |

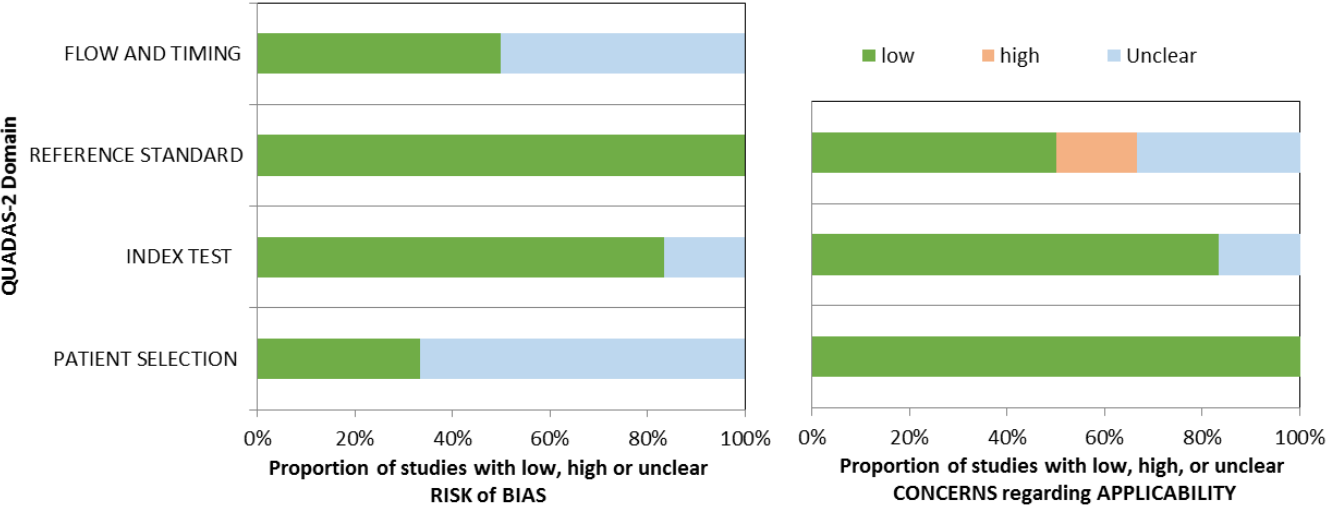
NA: Not available

Web Table 2: Odds ratios from logistic regression models of the association of impaired renal function (GFR) with serum markers of renal function

| Data | Variables in the model | N (N events) | Variable [†] | OR (95% CI) | p | AUC (95% CI) |
|----------------------------------------------------------------------------------------------------------------------------------|---------------------------|--------------|-----------------------|------------------|--------|----------------------|
| Barnfield (1 st measure per person) | Cystatin C | 83 (19) | Cystatin C | 9.0 (3.1, 26.0) | <0.001 | 0.862 (0.775, 0.950) |
| | Creatinine | 83 (19) | Creatinine | 2.2 (1.3, 3.8) | 0.006 | 0.681 (0.521, 0.840) |
| | Cystatin C and creatinine | 83 (19) | Cystatin C | 8.0 (2.7, 24.4) | <0.001 | 0.860 (0.772, 0.948) |
| | | | Creatinine | 1.5 (0.8, 2.8) | 0.214 | |
| Blufpand (1 st measure per person) | Cystatin C | 43 (3) | Cystatin C | 4.6 (1.1, 19.3) | 0.039 | 0.792 (0.427, 1.000) |
| | Creatinine | 43 (3) | Creatinine | 0.4 (0.1, 1.7) | 0.219 | 0.696 (0.270, 1.000) |
| | Cystatin C and creatinine | 43 (3) | Cystatin C | 4.7 (1.1, 20.5) | 0.041 | 0.883 (0.692, 1.000) |
| | | | Creatinine | 0.4 (0.1, 1.9) | 0.226 | |
| Lankisch (1 st measure per person) | Cystatin C | 80 (16) | Cystatin C | 7.5 (3.0, 18.9) | <0.001 | 0.915 (0.829, 1.000) |
| Barnfield, Blufpand and Lankisch (1 st measure per person, also including an indicator variable for study) | Cystatin C | 206 (38) | Cystatin C | 7.4 (4.0, 13.8) | <0.001 | 0.890 (0.828, 0.951) |
| Barnfield, Blufpand and Lankisch (allowing for the multiple measures per person with study as a random effect) | Cystatin C | 407 (126) | Cystatin C | 9.3 (5.8, 14.9) | <0.001 | 0.906 (0.872, 0.940) |
| Barnfield, Blufpand and Lankisch, age 0-4y (1 st measure per person, also including an indicator variable for study) | Cystatin C | 72 (10) | Cystatin C | 15.0 (3.1, 71.9) | 0.001 | 0.945 (0.895, 0.996) |
| Barnfield, Blufpand and Lankisch, age 5-12y (1 st measure per person, also including an indicator variable for study) | Cystatin C | 76 (11) | Cystatin C | 6.1 (2.2, 16.7) | <0.001 | 0.855 (0.729, 0.981) |
| Barnfield and Lankisch, age ≥13y (1 st measure per person, also including an indicator variable for study) | Cystatin C | 58 (17) | Cystatin C | 9.1 (2.6, 32.1) | 0.001 | 0.855 (0.747, 0.964) |

Notes: The GFR reference standard was dichotomised at GFR 80 ml/min/1.73m². † Cystatin C and Creatinine were log transformed due to skewed distributions and converted into z-scores. The z-scores have a mean of zero and standard deviation (SD) of one, enabling the comparison for an equivalent one SD change in each serum marker of renal function measurement. The Gronroos study was excluded from models because there were no events of GFR<80 ml/min/1.73m² for the first measure per person. Creatinine data were not available for analysis in our IPD dataset for the Lankisch study as we believe it may have also been used to calculate GFR. The Blufpand study was dropped from the combined model age ≥13y because there were no events in this study for this age group, this resulted in three people being dropped from this model.

Web Figure 1: Proportion of studies rated as high, low or unclear for each QUADAS-2 bias and applicability domains



Web Appendix: Data collection form

It would be very helpful if you could provide data based on the following structure.

However, we will accept data in any format which we will re-structure as necessary.

1. Underlying tumour type

Diagnosis under treatment, coded as

- 1 = Acute lymphoblastic leukaemia
- 2 = Acute myeloid leukaemia
- 3 = Other leukaemia
- 4 = Hodgkins lymphoma
- 5 = Non-Hodgkins lymphoma
- 6 = Low-grade brain tumour (I-II)
- 7 = High-grade brain tumour (III-IV)
- 8 = 'High risk' neuroblastoma
- 9 = Other neuroblastoma
- 10 = Retinoblastoma
- 11 = Wilm's tumour
- 12 = Other renal tumour
- 13 = Hepatoblastoma
- 14 = Other liver tumor
- 15 = Osteosarcoma
- 16 = Ewing's sarcoma
- 17 = Rhabdomyosarcoma
- 18 = Other sarcoma
- 19 = Germ cell/gonadal neoplasm
- 20 = Carcinoma/melanoma
- 21 = LCH
- 22 = Other
- 999 = Unknown

2. Chemotherapy type and date of last cycle

Specify the most recent chemotherapy cycle (in words/by acronym) (Will require a description of each chemotherapy protocol included from each study). Specify 'Unknown' if unknown.

3. Other treatment

Specify any other treatment being given at time of testing. Specify 'Unknown' if unknown.

4. Comorbidity

Specify any other comorbidity at time of testing. Specify 'Unknown' if unknown.

5. Age

Age in months at time of testing; 999 if missing

6. Gender

Male 1

Female 2

Data missing 999

7. Height

Height in cm; Data missing 999

8. Weight

Weight in kg; Data missing 999

9. BMI

Numerical; Data missing 999

10. Number of samples tested for Cystatin C

Numerical; Data missing 999

11. Numerical results for each Cystatin C test

Numerical; Data missing 999

12. Dates of each Cystatin C test

DD/MM/YYYY; Data missing 999

13. Number of samples tested using the reference standard

Numerical; Data missing 999

14. Numerical results for each reference standard assessment

Numerical; Data missing 999

15. Dates of each reference standard assessment

DD/MM/YYYY; Data missing 999

16. Other tests conducted

Text; Specify 'Unknown' if unknown.

17. Details of all other test results

Text; Specify 'Unknown' if unknown.

18. If the patient did not receive both index test and reference standard, reasons for this

Text; Specify 'Unknown' if unknown.